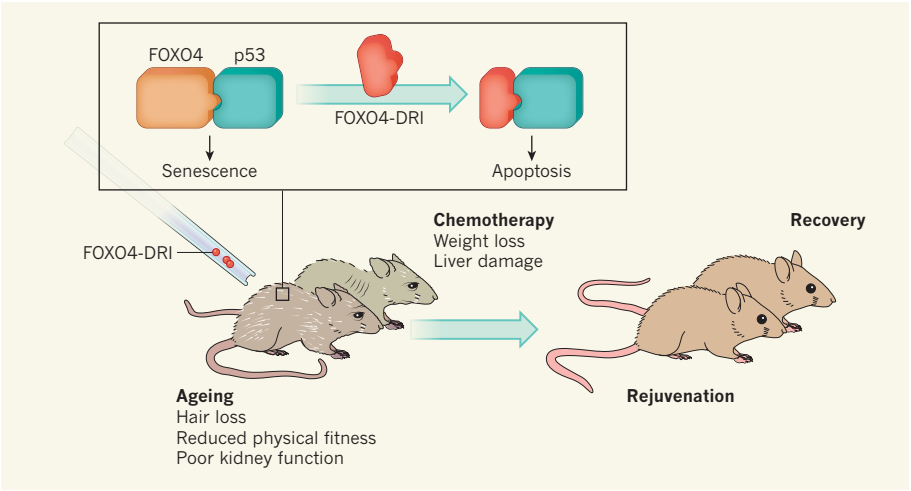

Figure 1 | Targeting a damaged cell population. Senescent cells, which cannot proliferate but release inflammatory signals, accumulate in old mice and mice treated with chemotherapy, causing a range of defects. Baar *et al.*[7] report that a complex of forkhead box protein O4 (FOXO4) and the protein p53 helps to maintain cell senescence. The authors developed a pharmacological peptide called FOXO4-DRI, which they injected into these mice. FOXO4-DRI competes with FOXO4 for p53 binding, pushing senescent cells to undergo apoptotic cell death. Administration of the drug ameliorated the effects of ageing and chemotherapy.

FOXO family members had no effect.

FOXO4 and some of its family members promote cell survival, in part through interactions with multiple protein partners[10]. On the basis of the authors' observations, FOXO4 can now be regarded as having a specialized role in promoting the survival of senescent cells. Interestingly, FOXO4 interacts with the protein p53, which is a well-established inducer of senescence[1]. The researchers therefore reasoned that this FOXO4–p53 interaction might be crucial for the survival of senescent cells, and that disrupting it would push such cells into apoptosis (Fig. 1). To test this, they synthesized a modified peptide fragment dubbed FOXO4-D-retro-inverso (FOXO4-DRI). This peptide lacks the normal transcriptional activity of FOXO4 but binds p53 more stably than does FOXO4 itself, thus competitively inhibiting the FOXO4–p53 interaction.

FOXO4-DRI efficiently killed senescent cells without affecting non-senescent cells when administered in a range of concentrations. Baar and colleagues suggest that the altered behaviour of p53 directly led to apoptosis. In addition, FOXO4-DRI might perturb the activity of one or more of the other FOXO4 binding partners involved in the survival of senescent cells[10]. Because relatively little is known about FOXO4 in general, and even less about its role in senescence in particular, it is hard to guess what the other potential effects of FOXO4-DRI might be — more research on this is needed.

Notably, the concentration window in which FOXO4-DRI selectively kills senescent cells was broader than that in which a BCL-2 inhibitor had the same effect. Moreover, it is known[11] that FOXO4 is expressed at only low levels in most tissues, and that mice lacking the *Foxo4* gene have no overt defects[11]; this suggests that FOXO4 disruption might not cause too much damage to healthy tissues if administered in mammals. Together, these features make FOXO4-DRI an attractive senolytic peptide.

Baar *et al.* examined the effects of FOXO4-DRI in mice in which cells that express a marker of senescence, the gene $p16^{Ink4a}$, were genetically engineered to emit light[12]. The authors treated the mice with doxorubicin, a drug that is widely used in chemotherapy. Doxorubicin can cause senescence and commonly has toxic side effects in mice and humans, including liver damage and weight loss. After doxorubicin administration, serial FOXO4-DRI treatments reduced the number of light-emitting, senescent cells and neutralized the drug's toxic effects.

The researchers next examined the effect of the peptide on ageing in two-year-old mice and in mice in which a genetic mutation causes premature ageing. In both, $p16^{Ink4a}$-expressing cells were again programmed to produce light. FOXO4-DRI reduced luminescence, restored juvenile traits such as greater hair density and high levels of voluntary physical activity, and protected animals of both strains from progressive loss of kidney function.

Baar and colleagues' results reinforce the concept that senolysis can prevent and reverse the severity of ageing-associated defects and the side effects of chemotherapy. Senolytic strategies could also be beneficial in treating cancer. Chemotherapeutic agents can induce senescence in susceptible cancer cells — for example, those in which p53 or $p16^{Ink4a}$ function normally (these genes are frequently mutated in cancer, so this is not always the case). Subsequent treatment with a senolytic agent might help to kill senescent tumour cells. This would not only diminish the effects of the SASP, which could promote tumour

50 Years Ago

Mr Anthony Wedgwood Benn, Minister of Technology, seems hopeful that Britain's application to join the Common Market may help to limit the flow of qualified manpower to the United States. Speaking at a symposium … on "Aspects of the Brain Drain", he said that the continent would become a magnet at least as powerful as the United States or the Soviet Union. Joint projects such as ELDO and Concorde were all very well, he suggested, but it was not only by big science that Europe could be made a good place to work in. The universities and industry, and people's attitudes towards them, were the really critical things … Mr Benn outlined the possible approaches to the problem. No forms of restriction appealed to him, either of the free motion of people or the freedom of other people to advertise for emigrants.
From *Nature* 20 May 1967

100 Years Ago

Pure "blood charcoal" is a reagent of considerable importance to the physiological chemist. It is not only required from the decolorisation of liquids, but also for selective adsorption in an important series of quantitative estimations of animal fluids. My Stock of Merck's blood charcoal is nearly exhausted, and I cannot obtain a supply of any homemade article that is suitable. I should be most grateful if any of your readers could give me any information as to the method of preparation of blood charcoal, or the name of a firm that would be willing to manufacture and supply the article. Material as good as Merck's would command a ready sale at home as well as in America, where they have had to abandon rapid and accurate methods of analysis owing to the lack of the necessary charcoal.
From *Nature* 17 May 1917